

# **Automatically Computed ECG Algorithm for the Quantification of Myocardial Scar and the Prediction of Mortality**

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## Abstract (250)

**Background:** Myocardial scar is associated with adverse cardiac outcomes. The Selvester QRS-score was developed to estimate myocardial scar from the 12-lead ECG, but its manual calculation is difficult. An automatically computed QRS-score would allow identification of patients with myocardial scar and an increased risk of mortality.

**Objectives:** To assess the diagnostic and prognostic value of the automatically computed QRS-score.

**Methods:** The diagnostic value of the QRS-score computed automatically from a standard digital 12-lead was prospectively assessed in 2'742 patients with suspected myocardial ischemia referred for myocardial perfusion imaging (MPI). The prognostic value of the QRS-score was then prospectively tested in 1'151 consecutive patients presenting to the emergency department (ED) with suspected acute heart failure (AHF).

**Results:** Overall, the QRS-score was significantly higher in patients with more extensive myocardial scar: the median QRS-score was 3 (IQR 2-5), 4 (IQR 2-6), and 7 (IQR 4-10) for patients with 0%, 5-20% and >20% myocardial scar as quantified by MPI ( $p < 0.001$  for all pairwise comparisons). A QRS-Score  $\geq 9$  ( $n=284$ , 10%) predicted a large scar defined as >20% of the LV with a specificity of 91% (95%CI 90-92%). Regarding clinical outcomes in patients presenting to the ED with symptoms suggestive of AHF, mortality after 1 year was 28% in patients with a QRS-score  $\geq 3$  as opposed to 20% in patients with a QRS-score  $< 3$  ( $p=0.001$ ).

**Conclusions:** The QRS-Score can be computed automatically from the 12-lead ECG for simple, non-invasive and inexpensive detection and quantification of myocardial scar and for the prediction of mortality.

## Introduction

Myocardial scar is associated with heart failure and worse outcome.<sup>1</sup> Myocardial scar also provides the substrate for reentrant ventricular arrhythmias and sudden cardiac death.<sup>2</sup> In order to improve survival and reduce morbidity, better strategies for identification and risk stratification of patients with heart failure and myocardial scar are an unmet clinical need.<sup>3</sup>

The gold standard for identification and quantification of myocardial scar are cardiac imaging techniques such as cardiovascular myocardial resonance imaging (CMR)<sup>4</sup> or myocardial perfusion imaging (MPI)<sup>5</sup>. However, these techniques have relevant limitations as risk stratification tools, since they are neither bedside tests nor widely available due to the costs and clinical expertise required. Preferably, an initial screening should involve simpler, cheaper and universally available tests, that may empower general practitioners and reduce the need for specialist referral, which could help to decrease the current fragmentation in clinical care.

The standard 12-lead ECG is a universally available, inexpensive test that would fulfill these requirements. Traditionally, myocardial scar was assessed qualitatively in the 12-lead ECG focusing on the presence of Q-waves.<sup>6</sup> More recently, the Selvester QRS-score was developed based on computer simulation.<sup>7,8</sup> The idea of the scoring system is to detect and quantify myocardial scar from the 12-lead ECG by measuring changes in Q-, R-, and S-wave duration and amplitudes and morphologies.<sup>7,8</sup> Later, modified criteria were suggested to be used in the presence of ECG confounders such as bundle branch blocks or LV hypertrophy.<sup>9</sup> In patients with left ventricular (LV) systolic dysfunction and heart failure, the extent of myocardial scar as assessed by the QRS-score has been shown to predict survival and the progression of symptoms.<sup>10,11</sup> Manual calculation of the QRS-score is difficult, tedious and may take up to 15 minutes per ECG,<sup>12</sup> thereby limiting its application in clinical practice. This problem could be overcome by the development of automated algorithms for calculation of the QRS-score using digital ECG data.<sup>13,14</sup> However, to the best of our knowledge, the automated QRS score and its

association with the extent of myocardial scar has never been prospectively validated against an imaging gold-standard.

The simple, non-invasive, and inexpensive detection and quantification of myocardial scar would be particularly helpful in the management of patients presenting with the two cardinal symptoms related to cardiac disease: chest discomfort and suspected myocardial ischemia as well as shortness of breath and suspected acute heart failure. We therefore performed a diagnostic study in two distinct large cohorts to examine the diagnostic and prognostic value of the QRS-score. Our aim was to determine (a) the association of the Selvester QRS-score automatically computed from the standard 12-lead ECG with the extent of myocardial scar as quantified by myocardial perfusion imaging (MPI), and (b) the prognostic value of the QRS-score to predict all-cause mortality during long-term follow-up in patients presenting to the ED with shortness of breath.

## **Methods**

### **Patient Population Myocardial Perfusion Imaging Cohort: BASEL VIII Study**

We prospectively enrolled consecutive patients referred to the University Hospital Basel for the evaluation of suspected myocardial ischemia by rest/stress myocardial perfusion imaging (MPI) for the “Biomarkers and ECG signals in exercise-induced myocardial ischemia (BASEL VIII)” study (ClinicalTrials.gov registry, number NCT01838148).<sup>15,16</sup> The authors designed the study, gathered, and analysed the data according to the STARD guidelines for studies of diagnostic accuracy (Supplemental Methods).

### **MPI acquisition and interpretation protocol**

Patients underwent routine rest/stress imaging using either a dual isotope (201Tl for rest, 99mTc sestamibi for stress) MPI protocol or a protocol with 99Tc for both examinations<sup>17</sup>. A standardized, stepwise, and symptom-limited bicycle exercise stress testing or a pharmacological stress testing protocol was performed.<sup>18</sup> MPI were evaluated by an expert team consisting of a cardiologist and a nuclear medicine physician and scored semi-quantitatively using a 17 segment bull’s eye scheme with a 5-point scale (0 = normal. 1 = mildly reduced tracer uptake. 2 = moderately reduced tracer uptake. 3 = severely reduced tracer uptake. 4 = no uptake).<sup>18</sup> Summed stress scores (SSS) and summed rest scores (SRS) were computed by adding the scores of the 17 segments in the stress and rest images respectively. Left ventricular ejection fraction (LVEF) was computed from post-stress gated images. The adjudication of the presence or absence of myocardial scar was based on the number of non-reversible segments (stress-rest score combinations of 4-4, 4-3, 3-3, 3-2, or 2-2) was summed up and used as a surrogate of the extent of myocardial scar size as described previously, with each non-reversible segment representing approximately 5% of myocardial scar.<sup>19</sup>

### **Patient Population Acute Decompensated Heart Failure Cohort: BASEL V Study**

We prospectively enrolled patients with symptoms suggestive of acute heart failure (AHF) presenting to the ED of the University Hospital Basel for the “Basics in acute shortness of breath

evaluation (BASEL V)” study (ClinicalTrials.gov registry, number NCT01831115).<sup>20,21</sup> A final diagnosis of AHF was adjudicated by two independent cardiologists using all available information pertaining to the individual patient after hospital discharge applying the guidelines of the European Society of Cardiology<sup>3</sup>. In case of disagreement, the case was reviewed by a third cardiologist who decided ultimately. Enrollment was independent of renal function, but patients with terminal renal failure on chronic renal replacement therapy were excluded for this analysis.

### **Follow-Up BASEL V Study**

Patients were contacted after 1 year by telephone calls or in written form. Furthermore, information was obtained by institutional chart review, the family physician’s records and the national registry on mortality. The primary prognostic endpoint was all-cause mortality during 1 year of follow-up.

### **Ethic’s approval**

BASEL VIII and BASEL V were carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committee. Written informed consent was obtained from all participating patients.

### **Recording of digital ECGs**

Resting 12-lead ECGs were acquired prior to the exercise stress test (BASEL VIII) or during standard clinical assessment of patients in the ED (BASEL V) using an AT-110 or CS-200 Excellence ECG device (Schiller AG, Baar, Switzerland). The digital ECG raw data was recorded using a minimal sampling rate of 500Hz, a minimal resolution of 5  $\mu$ V/bit and a minimal diagnostic signal bandwidth of 0.05Hz to 150Hz.

### **Principle of the Selvester QRS-score to quantify myocardial scar from the 12-lead ECG**

The Selvester QRS-score analysis protocol to quantify myocardial scar from the 12-lead ECG has previously been reported in detail.<sup>9,22</sup> In brief, ECGs are first classified for confounders into the 6 categories: left bundle branch block (LBBB), right bundle branch block (RBBB) and left anterior fascicular block (LAFB), isolated RBBB, isolated LAFB, left ventricular hypertrophy (LVH) or no

confounders. Second, points for Q-, R-, and S-wave amplitudes, durations, amplitude ratios, and notches in 10 of the 12 standard ECG leads (excluding leads III and aVR) are awarded according to the ventricular conduction/hypertrophy type. With a total of 54 criteria, a maximum QRS-score of 32 points can be reached, with each point representing 3% of the LV with myocardial scar. In addition, age and sex adjustments are made to the score criteria, as the normal limits of Q-, R-, and S-wave amplitudes and durations may differ by age and sex. For illustration and better understanding of the Selvester QRS-score, a sample scoring sheet and additional details are provided within the online supplemental appendix.

### **Automated calculation of the Selvester QRS-score**

The raw data of the digital 12-lead ECG was analyzed using the Schiller ECG analysis program (ETM V01.12.09.00, Schiller AG, Baar, Switzerland). Automated Q-, R-, and S-amplitude and duration measurements along with diagnostic statement codes were extracted and used for analysis. The criteria used to automatically classify ECG confounder types for QRS scoring have been published before<sup>14</sup> and are listed in the online supplemental appendix.

### **Statistical analysis**

Continuous variables are presented as mean (standard deviation) or median (interquartile range [IQR]); categorical variables, as numbers and percentages. Differences in baseline characteristics between patients were assessed using the Mann-Whitney test for continuous variables and the Pearson Chi Square test for categorical variables. Receiver-operating-characteristic (ROC) curves were constructed to assess the diagnostic accuracy of the QRS-score to diagnose a myocardial scar as adjudicated based on MPI. Survival according to QRS-score categories was plotted in Kaplan-Meier curves. The log-rank test was used to assess differences in mortality between groups. We used univariate Cox proportional hazard analysis to compute hazard ratios and 95% confidence intervals of the QRS-score to predict all-cause mortality and cardiovascular re-hospitalization. The model was further adjusted for the following established predictors of death to assess for independent prognostic value of the QRS-score (with dichotomous cut-points selected

where appropriate): age  $\geq 70$ , gender, dyspnea NYHA IV vs. II and III vs. II, QRS duration  $\geq 120$ ms, creatinine  $\geq 105$   $\mu\text{mol/l}$ , heart rate  $\geq 80$  bpm and the presence of diabetes mellitus, atrial fibrillation or LBBB.

All hypothesis testing was two-tailed and p-values  $< 0.05$  were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (SPSS Inc, Chicago, IL) and the R statistical package (MathSoft, Seattle, WA).



## **Results**

### **Enrolment and characteristics of patients referred for myocardial perfusion imaging**

#### **(BASEL VIII Study)**

From January 2010 to November 2014, a total of 4'219 unselected patients undergoing evaluation of suspected exercise inducible myocardial ischemia by myocardial perfusion imaging (MPI) were prospectively enrolled. Patients without a digital 12-lead ECG were excluded from analysis (n=1'002), as were patients with non-specific bundle branch block (NBBB, n=99) and ventricular pacing (n=57), which precluded automated calculation of the QRS-Score. Furthermore, patients with no SRS-score available, meaning patients with only stress imaging (n=319) were excluded, leaving 2'742 patients for analysis (Supplemental Figure 1).

Baseline characteristics of the patients are shown in Table 1. 32% of the patients had a history of myocardial infarction (MI) with a median time interval from MI to enrolment of 3.4 years (IQR 0.53-10.5 years).

Overall, no evidence of myocardial scar as quantified by MPI was seen in 62% of the patients. In 32% of the patients, the extent of myocardial scar was 5-20% and in 6% of the patients, more than 20% myocardial scar was present.

#### **Levels of the QRS-score in the MPI cohort**

The median QRS-score was 3 (IQR 2-6), representing an estimated LV scar of 9% (IQR 6-18%). Baseline characteristics of the patients stratified for QRS-scores  $\geq$  or  $<$  the median QRS-score of 3 are shown in Table 1. Patients with a QRS-score  $\geq$  3 more often had a history of coronary artery disease (CAD), MI and revascularization. The left ventricular ejection fraction (LVEF) as measured by MPI was significantly lower in patients with higher QRS-scores (all p-values  $<$  0.001).

#### **Association of the QRS-score with the extent of myocardial scar**

As shown in Figure 1, the QRS-score was significantly higher in patients with more extensive myocardial scar as quantified by MPI: for patients without myocardial scar, the median QRS-score

was 3 (IQR 2-5), for patients with 5-20% myocardial scar, the median QRS-score was 4 (IQR 2-6), and for patients with more than 20% myocardial scar, the QRS-score was 7 (IQR 4-10,  $p < 0.001$  for all pairwise comparisons). Of all patients with myocardial scar, 89% had a QRS-score  $\geq 1$ , resulting in a sensitivity of 94% (95%CI 90-97%) for the detection of any myocardial scar. Diagnostic accuracy of the QRS-score for the detection of any myocardial scar as quantified by the AUC was 0.60 (95%CI 0.58-0.62). For the detection of a myocardial scar  $> 20\%$  the AUC was 0.73 (95%CI 0.69-0.78). A QRS-Score  $\geq 9$  ( $n=284$ , 10%) predicted a large scar defined as  $> 20\%$  of the LV with a specificity of 91% (95%CI 90-92%).

### **Impact of ECG confounders on the association with myocardial scar**

The ECG was free of confounders in 82% of patients. Of those with ECG confounders, complete LBBB was present in 3.4%, combined RBBB & LAFB in 2.2%, isolated RBBB in 3.2%, isolated LAFB in 3.0%, and LVH in 5.8% of all cases. Presence and type of ECG confounders of cardiac de- and repolarization resulted in significant changes of the QRS-score. Median QRS-scores for the different ECG confounder groups overall and according to the extent of myocardial scar are shown in Table S1. Of particular note, the presence of LAFB either in isolation or in conjunction with RBBB resulted in higher QRS-scores compared to all other groups.

### **Diagnostic value of the QRS-score to detect a reduced LVEF $<35\%$**

A reduced LVEF  $< 35\%$  was found in 209 patients (8%). As shown in Figure 2, the QRS-score was significantly higher in patients with reduced LVEF: for patients with LVEF  $<35\%$ , the median QRS-score was 5 (IQR 3-9) and for patients with more than 55% LVEF, the QRS-score was 3 (IQR 1-5,  $p < 0.001$ ). For patients with a QRS-score  $\geq 9$  (10%), the specificity to detect a reduced LVEF was 91% (95%CI 90-92%) and sensitivity was 24% (95%CI 19-31%). On the other hand, a QRS-score of 0 (12%) had a sensitivity of 94% (90-97%) and a specificity of 13% (95%CI 12-14%) to rule-out a reduced LVEF  $<35\%$ .

## **Enrolment and characteristics of patients with symptoms suggestive of AHF (BASEL V Study)**

From September 2001 to January 2013, a total of 2'130 patients with symptoms suggestive of AHF presenting to the ED were prospectively enrolled. Patients without a digital 12-lead ECG were excluded from analysis (n=881), as were patients with NBBB (n=84) and ventricular pacing (n=14), leaving 1'151 patients for analysis (Figure S2). Overall, 61% of patients had a final adjudicated diagnosis of AHF.

### **Levels of the QRS-score in the AHF cohort**

Overall, the median QRS-score was 3 (IQR 1-6) equal to an estimated LV scar of 9% (3-18%). Baseline characteristics of the patients stratified for QRS-score levels  $\geq$  or  $<$  the median value of 3 are shown in Table 2. Similarly, to the Basel VIII cohort, patients with higher QRS-score had more often a history of CAD, MI and revascularization and had significantly higher B-type natriuretic peptide (BNP) levels at presentation (345 vs 605 ng/l,  $p < 0.001$ ). A QRS-score  $\geq 3$  was associated with a higher probability for a final adjudicated diagnosis of AHF (67% vs. 55%,  $p < 0.001$ ).

### **Diagnostic value of the QRS-score to detect a reduced LVEF $< 35\%$ in patients with suspected AHF**

The LVEF was assessed by transthoracic echocardiography (TTE) in 653 patients. A reduced LVEF  $< 35\%$  was found in 21% of the patients. As shown in Figure 2, the QRS-score was significantly higher in patients with reduced LVEF: for patients with LVEF  $< 35\%$ , the median QRS-score was 4 (IQR 2-7), for patients with 35-55% LVEF, the median QRS-score was 3 (IQR 1-6), and for patients with more than 55% LVEF, the QRS-score was 2 (IQR 1-5,  $p < 0.001$ ).

Similar to the results in the BASEL VIII cohort, a QRS-score  $\geq 9$  (11%) had specificity to detect a reduced LVEF by TTE of 91 % (95%CI 89-94%) with a corresponding sensitivity of 20% (95%CI 14-28%). On the other hand, a QRS-score of 0 (18%) had a sensitivity of 89% (95%CI 82-94%) and a specificity of 16% (95%CI 13-20%) to rule-out a reduced LVEF  $< 35\%$ .

### **Prognostic value of the QRS-score for the prediction of mortality during follow-up**

During a mean follow-up time of 430 days, there were 367 deaths (32%) in the whole cohort. All-cause mortality after 1 year was 28% in patients with a QRS-score  $\geq 3$  as opposed to 20% in patients with a QRS-score  $<3$  in Kaplan-Meier analysis ( $p=0.001$  Figure 3A). The difference in mortality could be observed as early as after 30 days with mortality rates of 9% vs. 5% in patients with a QRS-score  $\geq 3$  vs.  $< 3$  ( $p=0.02$ ). When assessing only patients with a final adjudicated diagnosis of AHF (61% of the overall cohort) the all-cause mortality rates at 1-year follow-up were 32% vs. 23% for patients with a QRS-score  $\geq 3$  and  $< 3$  ( $p = 0.01$ ). The observation of higher mortality rates at 30 and 360 days in patients with a QRS-score  $\geq 3$  was confirmed in patients with and without ECG confounders present in the 12-lead ECG (Table S2). In univariable cox proportional hazard analysis QRS-score as a continuous variable (per 3-point increase) was significantly related with all-cause mortality (Hazard Ratio, 1.11, 95%CI 1.02-1.22,  $p=0.02$ ). When using a dichotomous cut-off for presence of scar defined by the median QRS-score of  $\geq 3$ , there were 48% more deaths compared to patients with a QRS-score  $< 3$  (Hazard Ratio 1.48, 95%CI 1.16-1.89,  $p=0.001$ ). After adjusting for important clinical factors (including age, diabetes mellitus, dyspnea and renal failure) and ECG parameters (QRS duration, heart rate, atrial fibrillation and LBBB) in multivariable analysis, a QRS-score  $\geq 3$  remained an independent predictor of mortality (Hazard Ratio 1.42, 95%CI 1.10-1.83, for QRS  $\geq 3$  versus  $<3$ ,  $p=0.006$ , Table 3).

### **QRS-score association with cardiovascular re-hospitalization**

During follow-up, a total of 248 patients (22%) required a re-hospitalization due to congestive heart failure (CHF) or another cardiac reason. There were 45% more re-hospitalizations in patients with a QRS-score  $\geq 3$  (HR 1.45, 95%CI 1.12-1.89,  $p=0.005$ , Figure 3B). The QRS-score as a continuous variable (per 3 points increase) was also significantly related with first occurrence of re-hospitalization during 360 days (HR 1.18, 95%CI 1.08-1.30,  $p=0.001$ ). After adjusting for clinical factors and ECG parameters, a QRS-score  $\geq 3$  was an independent predictor of re-hospitalization

along with the presence of atrial fibrillation, diabetes mellitus and renal failure at presentation (Table S3).

## Discussion

In two large prospective diagnostic studies, we aimed (a) to assess the association of the QRS-score automatically computed from the 12-lead ECG with the extent of myocardial scar as quantified by MPI in 2742 patients and (b) to study the prognostic value of the QRS-score to predict mortality during long-term follow-up in 1151 patients presenting to the ED with symptoms suggestive of AHF.

We report three major findings: First, QRS-scores at presentation were significantly higher in patients with more extensive myocardial scar on MPI. The diagnostic accuracy of the QRS-score for the detection of any myocardial scar on MPI as quantified by the AUC was 0.60 and increased to 0.73 for the detection of >20% myocardial scar. Second, higher QRS-scores predicted a reduced LVEF in both cohorts. A QRS-score  $\geq 9$  had a specificity of 91% in both cohorts to detect a LVEF <35%. Third, the QRS-score was a powerful predictor of all-cause mortality and re-hospitalization in patients presenting to the ED with symptoms suggestive of AHF independent of important other clinical and ECG factors. All-cause mortality after 1 year was 28% in patients with a QRS-score  $\geq 3$  as opposed to 20% in patients with a QRS-score <3 ( $p < 0.001$ ).

These findings extend and corroborate previous data on the possible clinical utility of the QRS-score to predict the presence of myocardial scar.<sup>13,23–27</sup> This study has important methodological strengths differentiating it from previous studies on the QRS-score, including but not limited to its prospective design, the automated calculation of the updated QRS scoring system, the applicability in the presence of traditional ECG confounders and the use of the adjusted criteria for age and sex. Furthermore, to the best of our knowledge, this is the largest prospective validation studying the association of the QRS-score with the extent of myocardial scar as quantified by a cardiac imaging technique.

The diagnostic performance of the QRS-score to detect myocardial scar in this study was similar to that reported elsewhere using CMR.<sup>13,23–25,27</sup> Previously, a wide range of diagnostic accuracy to detect myocardial scar was shown with AUC between 0.62 and 0.91.<sup>13,23,27</sup> The reasons for this

variety are manifold. First, in the early beginning, Selvester and Coworkers<sup>8,28</sup> developed the QRS-score in the non-reperfusion era for acute MI in comparison to post-mortem histopathological analysis. It is therefore possible that the score best reflects acute scar resulting from non-reperfused fatal myocardial infarctions rather than chronic, remodelled myocardial scar late after AMI. This hypothesis was further supported by CMR studies, as also stronger correlation for ECG estimated scar was seen in patients early after a first MI.<sup>24,26</sup> Second, the association between the QRS-score and the extent of myocardial scar on MPI is more robust in patients without ECG confounders. Hence, the diagnostic performance of the QRS score varies depending on the prevalence of ECG confounders in a cohort. This proportion of ECG confounders was 18% in our study, and remarkably higher compared to some of the previous studies, which enrolled as little as 9 patients (6%) with ECG confounders.<sup>29</sup> With regards to the different subgroups of ECG confounders, we could confirm the previous observation that the algorithm overestimated the extent of myocardial scar particularly in patients with isolated LAFB or LAFB & RBBB.<sup>13,27</sup> As opposed to the QRS-score in patients without ECG confounders, the modified QRS scoring system in the presence of conduction defects was created based on computer simulation and has never been validated with post-mortem analysis.<sup>9</sup> Given that the presence of LAFB significantly affects leads  $V_4$ - $V_6$ , Wieslander et al.<sup>27</sup> made an attempt to modify the scoring system by excluding points derived from leads  $V_4$ - $V_6$  in LAFB patients, which improved the AUC for scar detection from 0.62 to 0.67. Third, the manual calculation of the QRS-score is difficult, tedious and may take up to 15 minutes per ECG.<sup>12</sup> Accordingly, results were often highly operator-dependent and its application in clinical practice was limited. Using an automated algorithm for calculation of the QRS-score from digital ECG data, the method is much more robust and can be easily applied in clinical practice.<sup>14,30</sup> Our study is the first to prospectively validate an automatically computed QRS-score against an imaging gold standard. The similar diagnostic accuracy compared to studies using manual calculation done by extensively trained and highly experienced ECG readers

is important and supports the suitability of the automated QRS score for a broad clinical application.<sup>13,23,27</sup>

The extent of myocardial scar is correlated with LVEF. Accordingly, higher QRS-scores predicted a reduced LVEF and a QRS-score  $\geq 9$  had a specificity of  $>90\%$  in both cohorts to detect a LVEF  $<35\%$ . Given that current guidelines for ICD-implantation for primary prevention of sudden cardiac death focus predominantly on a LVEF  $<35\%$ , the QRS-score may serve as a simple screening tool in general medical populations to identify patients potentially at risk that might benefit from further work-up with echocardiography.

Beyond its diagnostic utility in the detection of myocardial scar, the QRS-score is a simple, inexpensive and easily implementable method for the prediction of clinical outcome. In our cohort of patients presenting with symptoms suggestive of AHF, those with a QRS-score above the median ( $\geq 3$ ) had a 48% higher risk of mortality and a 45% higher risk of re-hospitalization due to cardiovascular causes within 1-year after the index presentation. This is in line with previous observations made in studies investigating the prognostic value of the QRS-score in various other settings<sup>14,23,26,31,32</sup>. Similar to our results, a recent study showed that in 100 consecutive acute MI patients, a QRS-score  $\geq 3$  at hospital discharge was associated with significantly more deaths or hospitalizations for heart failure during follow-up compared with a QRS-score  $< 3$  (45% vs. 8%,  $p < 0.001$ ).<sup>32</sup> It is important to highlight that the incremental value of the QRS-score for risk stratification was independent of other important clinical and ECG factors including age and QRS duration.

It has to be mentioned that the QRS-score should not be seen as an alternative to imaging techniques. Rather, it should be used as an easily available additional screening tool for risk stratification in conjunction with all available other information. Particularly in the primary care setting, the QRS-score provides a simple, non-invasive and inexpensive tool for the general practitioner for the identification of patients with so far undetected myocardial scar and an increased risk. A QRS-score  $\geq 9$  in a patient with no known cardiac history should trigger referral



to a cardiologist for additional workup. Doing so, it is a tool that may empower general practitioners in the delineation of a personalized management plan. It is possible that a further improvement of its performance can be achieved by refinement of some of the less specific criteria of the score (54 in total).<sup>27</sup> Our results also demonstrate that research focusing on advanced ECG technologies has the potential to remarkably increase the value of the surface 12-lead ECG in clinical cardiology.<sup>16,33</sup>

Potential limitations of the present study merit consideration. First, it is a matter of ongoing discussion, which cardiac imaging modality provides the most favorable characteristics for the detection and quantification of a myocardial scar.<sup>34</sup> While CMR provides higher spatial resolution and is therefore superior in the detection of very small myocardial scars,<sup>35</sup> it cannot be applied in patients with pacemakers and defibrillators, and is challenging to apply in patients with claustrophobia. As MPI has important logistic advantages compared to CMR, and as a direct comparison of MPI versus CMR using absolute scar quantification with necropsy as reference standard showed comparable performance of both techniques, MPI seemed well suited for the purpose of the current study using a semi-quantitative assessment of the extent of myocardial scar.<sup>34</sup> Second, the value of the QRS-score to predict mortality was assessed in ED patients with symptoms suggestive of AHF in our study. Further studies are needed to assess the prognostic value of the QRS-score in other patient populations, e.g. for risk stratification in the general population or in patients after AMI. Third, further research may improve the classification of borderline ECGs, e.g. the fine-tuning of the definition of LBBB.<sup>36</sup> Fourth, it is possible that beat-to-beat variation in the QRS complex may lead to different numbers of points to be assigned to a lead depending on which beat is evaluated. In order to limit bias and error, we used a computer-generated median beat.

In conclusion, the QRS-Score, a marker quantifying myocardial scar, can be automatically computed from the 12-lead ECG. It is associated with the extent of myocardial scar as quantified by MPI. In addition, the QRS-score independently predicts all-cause mortality in patients

presenting with symptoms suggestive of AHF and helps categorizing patients into those with reduced and normal ejection fraction. Therefore, the QRS-score provides a simple, non-invasive and inexpensive tool for the identification of patients at risk and thereby may be an important contributor in the delineation of a personalized management plan.

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Table 1		Baseline characteristics of the patients with suspected exercise inducible myocardial ischemia (BASEL VIII)		
	All patients (n=2'742)	QRS-score		p-Value
		<3 (n=1'042)	≥3 (n=1'700)	
Age – years	68 (59-75)	68 (60-75)	68 (59-76)	0.90
Male gender – no. (%)	1938 (71)	728 (70)	1210 (71)	0.49
Risk factors – no. (%)				
Hypertension	2285 (83)	870 (83)	1415 (83)	0.90
Hypercholesterolemia	2057 (75)	777 (75)	1280 (75)	0.70
Diabetes	726 (27)	272 (26)	454 (27)	0.76
Current smoking	513 (19)	180 (17)	333 (20)	0.15
History of smoking	1175 (43)	453 (43)	722 (42)	0.63
History – no. (%)				
Coronary artery disease	1412 (51)	504 (48)	908 (53)	0.01
Previous MI	890 (32)	277 (27)	613 (36)	<0.001
Previous revascularization	1275 (46)	459 (44)	816 (48)	0.05
Peripheral artery disease	285 (10)	93 (9)	192 (11)	0.06
Previous stroke	249 (9)	94 (9)	155 (9)	0.99
ECG findings – no. (%)				
Q-waves	318 (12)	59 (6)	259 (15)	<0.001
LBBB	94 (3)	35 (3)	59 (3)	0.96
RBBB+LAFB	60 (2)	9 (1)	51 (3)	<0.001
RBBB	89 (3)	38 (4)	51 (3)	0.41
LAFB	81 (3)	4 (0)	77 (5)	<0.001
LVH	158 (6)	74 (7)	84 (5)	0.02
No confounders	2260 (82)	882 (85)	1378 (81)	0.02
Body mass index (kg/m <sup>2</sup> )	27 [25-31]	27 [25-30]	27 [25-31]	0.25
MPI Findings				
Presence of any scar	1050 (38)	332 (32)	718 (42)	<0.001
Presence of > 20% scar	164 (6)	27 (3)	137 (8)	<0.001
LVEF (%)	54 [46-63]	56 [49-64]	53 [44-62]	<0.001
Laboratory findings				
hs-cTnT. ng/L	9 [6-16]	9 [5-15]	10 [6-17]	<0.001
Chronic medication				
ASA	1792 (65)	683 (66)	1109 (65)	0.90
Vitamin K antagonists	301 (11)	94 (9)	207 (12)	0.01
B-blockers	1652 (60)	611 (59)	1041 (61)	0.19
Statins	1718 (63)	655 (63)	1063 (63)	0.89
ACEIs/ARBs	1740 (63)	649 (62)	1091 (64)	0.34
Calcium antagonists	671 (24)	263 (25)	408 (24)	0.49
Nitrates	288 (11)	98 (9)	190 (11)	0.16

\*MI = myocardial infarction. ECG = electrocardiogram. LBBB = left bundle branch block. RBBB = right bundle branch block. LAFB = left anterior fascicular block. LVH = left ventricular hypertrophy. MPI = myocardial perfusion imaging. LVEF = left ventricular ejection fraction. Hs-cTn = high-

sensitivity cardiac troponin. ASA= Acetylsalicylic acid. ACEIs/ARBs = angiotensin converting enzyme inhibitor/angiotensin receptor blocker.



Table 2	Baseline characteristics of the patients with suspected acute decompensated heart failure (BASEL V)			
	All patients (n=1151)	QRS-Score		p-Value
		<3 (n=534)	≥3 (n=617)	
Age – years	77 [66. 83]	76 [65. 83]	77 [66. 84]	0.35
Male gender – no. (%)	593 (52)	261 (49)	332 (54)	0.12
Risk factors – no. (%)				
Hypertension	811 (71)	365 (68)	446 (74)	0.07
Hypercholesterolemia	397 (36)	177 (34)	220 (38)	0.23
Diabetes	282 (25)	113 (21)	169 (28)	0.01
Current smoking	236 (21)	108 (20)	128 (21)	0.90
History of smoking	511 (45)	229 (43)	282 (46)	0.39
History – no. (%)				
Coronary artery disease	415 (36)	162 (30)	253 (42)	<0.001
Previous MI	228 (21)	84 (16)	144 (25)	0.001
Previous revascularization	232 (21)	94 (18)	138 (23)	0.03
Peripheral artery disease	156 (14)	67 (13)	89 (15)	0.39
Previous stroke	146 (13)	61 (11)	85 (14)	0.23
ECG findings – no. (%)				
ST-segment deviation	57 (5)	23 (4)	34 (6)	0.42
T-wave inversion	80 (7)	44 (8)	36 (6)	0.14
LBBB	62 (5)	18 (3)	44 (7)	0.01
RBBB+LAFB	48 (4)	7 (1)	41 (7)	<0.001
RBBB	58 (5)	35 (7)	23 (4)	0.04
LAFB	39 (3)	2 (0)	37 (6)	<0.001
LVH	215 (19)	109 (20)	106 (17)	0.18
Norm	729 (63)	363 (68)	366 (59)	0.003
Adjudicated final diagnosis – no. (%)				
AHF	704 (61)	292 (55)	412 (67)	<0.001
Non-cardiac causes of dyspnea*	447 (39)	242 (45)	205 (33)	<0.001
Imaging Findings – no. (%)				
LVEF	55 [35. 60]	55 [40. 60]	50 [34. 60]	<0.001
Laboratory findings				
BNP. ng/l	476 [117. 1148]	345 [85. 857]	605 [159. 1359]	<0.001
Chronic medication – no. (%)				
ASA	417 (37)	192 (37)	225 (38)	0.73
Vitamin K antagonists	302 (27)	118 (22)	184 (31)	0.002
B-blockers	532 (48)	234 (45)	298 (50)	0.07
Statins	365 (33)	170 (32)	195 (33)	0.88
ACEIs/ARBs	762 (67)	367 (69)	395 (65)	0.11

Calcium antagonists	319 (29)	149 (28)	170 (29)	0.87
Nitrates	128 (12)	55 (11)	73 (13)	0.30

MI = myocardial infarction. ECG = electrocardiogram. LBBB = left bundle branch block. RBBB = right bundle branch block. LAFB = left anterior fascicular block. LVH = left ventricular hypertrophy.

MPI = myocardial perfusion imaging. CHF = congestive heart failure. LVEF = left ventricular ejection fraction. BNP = B-type natriuretic peptide. ASA= Acetylsalicylic acid. ACEIs/ARBs = angiotensin converting enzyme inhibitor/angiotensin receptor blocker.

\*Non-cardiac causes of dyspnea included predefined categories such as chronic obstructive pulmonary disease (COPD), asthma bronchiale, pneumonia, bronchitis, Influenza, hyperventilation, pulmonary embolism or cancer.

Table 3	Cox proportional hazard analysis for all-cause mortality at 360 days							
	Univariable cox regression				Multivariable cox regression			
	Hazard ratio	95% CI		p-Value	Hazard ratio	95% CI		p-Value
QRS-score ≥ 3	1.48	1.16	1.89	.001	<b>1.42</b>	<b>1.10</b>	<b>1.83</b>	<b>.006</b>
Gender (male)	1.08	0.85	1.36	0.53				
Age ≥ 70 (years)	2.90	2.10	4.02	< 0.001	<b>2.60</b>	<b>1.85</b>	<b>3.65</b>	<b>&lt; 0.001</b>
Diabetes mellitus	1.06	0.81	1.38	.68				
NYHA III (III vs. II)	1.97	1.11	3.51	.02	1.39	0.78	2.49	.27
NYHA IV (IV vs. II)	3.30	1.88	5.81	< 0.001	<b>2.37</b>	<b>1.34</b>	<b>4.20</b>	<b>0.003</b>
Atrial Fibrillation	1.31	1.02	1.69	.04	0.96	0.73	1.26	.77
QRS-width (ms)	1.30	0.99	1.70	.06				
High creatinine (≥105 mol/l)	2.25	1.78	2.86	< 0.001	<b>1.96</b>	<b>1.53</b>	<b>2.52</b>	<b>&lt; 0.001</b>
LBBB	2.15	1.45	3.20	< 0.001	<b>1.52</b>	<b>0.99</b>	<b>2.33</b>	<b>.05</b>
Heartrate ≥ 80 (bpm)	1.63	1.24	2.14	< 0.001	<b>1.63</b>	<b>1.23</b>	<b>2.17</b>	<b>0.001</b>

\*NYHA = New York Heart Association. LBBB = left bundle branch block. BPM = beats per minute.

**Figure 1**

**Boxplots for the distribution of the QRS-score according to the extent of myocardial scar on myocardial perfusion imaging.**

**Figure 2**

**Boxplots for the distribution of the QRS-score according to the left ventricular ejection fraction in (A) the BASEL VIII and in (B) the BASEL V cohort.**

**Figure 3A**

**Kaplan-Meier curves for all-cause mortality at 360 days displayed for QRS-score levels  $<3$  and  $\geq 3$**

**Figure 3B**

**Kaplan-Meier curves for cardiovascular re-hospitalization at 360 days displayed for QRS-score levels  $<3$  and  $\geq 3$**